Study Protocol and Statistical Analysis Plan

Study Title:

Developing a Working Memory Intervention for Craving in Opioid Use Disorder

Date: 9/9/2021

NCT#: NCT05086835

Protocol Title: *Developing a Working Memory Intervention for Craving in Opioid Use Disorder*

I. Background and Significance

Even when treated with methadone or buprenorphine maintenance, many people with opioid use disorder (OUD) continue to experience craving. Among both users of heroin and users of prescription opioids, mounting evidence shows that craving predicts return to use and undermines existing treatments for OUD, thus, the development of new interventions to reduce craving is a priority for addressing the opioid crisis (NIH HEAL Initiative Research Plan, 2019). Deficits in executive functioning, particularly working memory, are a central mechanism that undermines the ability to inhibit craving. Laboratory studies in non-clinical samples show that engaging in working memory tasks before or during a craving induction increases the ability to resist craving. This suggests that people with OUD may benefit from engaging in working memory tasks at the specific moment when craving occurs. Although previous research shows that working memory "training" does not improve clinical outcomes in OUD (Wiers, 2018), these studies have not delivered training at the moment that craving actually occurs in daily life. Thus, engaging in working memory tasks at the moment that craving occurs could presumably help individuals with OUD to manage this persistent symptom, but this has not been tested. Further, studies using Ecological Momentary Assessment (EMA) methods show that people with OUD can accurately track moment-to-moment fluctuations in craving in their daily lives (Preston et al., 2017), suggesting that it may be feasible to deliver interventions for craving in the moment when craving is reported. These converging lines of evidence indicate that it may be feasible to use a smartphone-based digital health intervention to help individuals with OUD manage craving in their daily lives, through the use of a mobile working memory intervention.

However, before such interventions can be tested, it is essential to collaborate with individuals who would actually use the intervention – adults with OUD – to gather their feedback on the parameters of this type of intervention. This process, often referred to as human-centered design (Yardley et al., 2015), involves collaborating with stakeholders to gauge their perceptions of the intervention, collect qualitative data on their impressions of what features of the intervention would be most helpful for the target symptom (craving), and provide an opportunity for stakeholders to suggest ways to make the intervention more credible, helpful, and engaging. Indeed, these three domains are significant predictors of ultimate engagement in digital interventions (Yardley et al., 2016). Thus, the goal of the human-centered design process in this study is to increase the likelihood that the final intervention will be relevant and useful for individuals with OUD.

Using the NIH Stage Model of Intervention Development, this study will consist of a Stage 1A project designed to gather feedback from adults receiving treatments for OUD (n = 20). This feedback will help our research team finalize a working memory intervention in preparation for a future Stage 1B trial using a randomized design.

II. Specific Aims

Objective #1: Assess attitudes about mobile health interventions in adults with opioid use disorders.

Objective #2: Collect feedback from participants regarding their perceptions of proposed components for an intervention to address craving in opioid use disorder.

Objective #3: Based on feedback from participants, refine proposed components for the development of a smartphone application to be used in a future study.

This study does not involve formal hypothesis testing; rather, the goal is to gain user input to inform the final development of a smartphone-based working memory intervention for opioid craving.

III. Subject Selection

Up to 25 participants will be recruited for the present study. We aim to have complete data for 20 participants, but will recruit up to 25 in order to allow for the possibility that some participants may drop out or be found ineligible after consenting to participation**.** Recruitment will take place at McLean Hospital's programs that provide treatment for opioid use disorder, including the Naukeag residential treatment program and the Alcohol, Drug, and Addiction Treatment Program (ADATP) at the main campus of McLean Hospital. Inclusion criteria include: a diagnosis of opioid use disorder, self-reported ability to use a smartphone, and age 18 or greater. Exclusion criteria include: lack of capacity to consent; current involuntary admission (for inpatients); acute psychosis; diagnosis of a neurological disorder or other brain disease affecting cognitive functioning; history of stroke; or cognitive deficits indicated by a score of less than 26 on the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005). Other than the MoCA, all exclusion criteria will be evaluated through a review of a participants' medical record and consultation with clinical staff.

Potential participants will be enter the study through two pathways: (1) self-selection based on posted advertisements and presentations by research staff at the beginning of clinical groups, or (2) invitation to participate from research staff, after introduction by a clinical staff member and the patient's agreement to meet with the Research Assistant. Regarding this second pathway, potential participants are identified via either (1) review of the electronic medical record of new admissions, or (2) referral from clinical staff. Prior to approaching any potential participants, a member of study staff will consult with the patient's treatment team to verify that they do not meet any exclusion criteria (e.g., for inpatients, that they are not hospitalized involuntarily), and to verify that the potential participant has been determined by the treatment team to have the capacity to consent. Once a potential participant is identified, a member of the study team (research assistant or PI) will be introduced to the potential participant by a member of the clinical staff. The study staff member will then meet in-person with the participant to provide a brief overview of the study. If the potential participant continues to express interest, a study session will be scheduled at the participant's convenience.

IV. Subject Enrollment

Participants will review the study fact sheet, provide verbal consent, and complete all study procedures in one study session lasting approximately one hour. If participants would like extra time to review the study fact sheet before deciding to participate, they may do so. Consent will be obtained via a review of the study fact sheet and discussion of study procedures immediately prior to the study session. A member of study staff (research assistant or PI) will meet with the participant to review the study fact sheet, answer questions about the study, and verbally explain study procedures. Participants may choose to verbally consent and begin participation, or they may choose to take a blank copy of the study fact sheet with them and to consider enrolling at a later date. There is no time limit on how long participants may choose to consider participation; however, participants will only be eligible to enroll in the study if they are still receiving treatment in one of the recruitment sites at McLean. Research staff will document that verbal consent was obtained, and will record participants' name and date of consent in a study-specific electronic database.

Participants will be fully informed of the nature of the risks involved during the informed consent process and will have the ability to discontinue and withdraw consent at any time without penalty. All study personnel will be trained in the appropriate care of human participants and will have completed the Collaborative Institutional Training Initiative (CITI) human subjects training, and research assistants will be closely supervised by the study PI. As part of the informed consent process, participants will be informed that if they feel uncomfortable responding to any question, they are free to choose not to respond or to express their discomfort.

V. Study Procedures

All study procedures will be conducted in a single study session lasting approximately one hour. In all sessions, participants will meet with members of study staff to review the informed consent fact sheet, complete brief assessment of cognitive functioning to verify eligibility (the MoCA), and then complete a qualitative interview to inform intervention development. Participants who complete this study will complete interviews that encompass the planning and design phases of intervention development. These interviews will assess their perceptions of smartphone-based interventions in general; their perceptions of smartphone-based interventions for substance use disorders; their existing strategies for managing craving in daily life; and their attitudes about the potential features of the working memory intervention for craving that is being developed.

Participants who complete this study will also provide feedback on specific components of the intervention being developed. To aid this goal, participants will view wireframes (non-functional mockups) of different intervention components, will try using "demonstration" versions of various app components using a study-specific iPod, and will be asked to provide feedback in response to various prompts about the acceptability of these components (e.g., clarity of instructions, flow from one screen to the next, presentation of feedback, etc). The intervention being developed is a working memory task that is based on a modified version of the game "Tetris," (or something similar to Tetris) which involves using visual-spatial memory to organize falling blocks. App components that participants will try out include the freely available game "Tetris" (https://apps.apple.com/us/app/tetris/id1491074310) and various games contained in an app called "mindLAMP" (https://docs.lamp.digital/privacy). Both apps involve short (1-2 minute) games that involve using working memory. Thus, we will ask participants about their perceptions of using a game like this for treatment of craving, their previous experience using this type of game, and the degree to which they would choose to use this type of intervention when experiencing opioid craving. At the conclusion of the study session, all participants will complete self-report measures of demographic information, perceptions of questions that assess craving on smartphones, and a self-report measure of task acceptability(a modified Credibility and Expectancy Questionnaire; Devilly et al., 2000). This self-report measure will include additional questions to assess perceived helpfulness and enjoyability of the intervention and will be administered electronically via REDCap (Harris et al., 2009). At the conclusion of the study visit, participants will be provided with one $25 gift card for their participation.

Measures to be used in this study include:

a. Montreal Assessment of Cognitive Functioning (MoCA)
b. Qualitative interview of craving, mobile interventions, and intervention feedback
c. Modified Credibility and Expectancy Questionnaire
d. Demographic Questionnaire
e. Daily Questions Survey

VI. Biostatistical Analysis

Variables collected as part of this study include: responses to open-ended questions collected as part of a qualitative interview (written down on a study-specific interview form), questionnaire data (collected electronically via REDCap; Harris et al., 2009), and results of the brief cognitive assessment (MoCA; conducted on pen and paper and recorded electronically). We will not analyze data from the demonstration apps. Formal statistical tests of hypotheses will not be conducted as part of this study, as the goal is to collect participant feedback to inform the development of a future smartphone-based intervention. Themes arising from qualitative data may be aggregated and summarized using a basic coding method such as the general inductive approach (Thomas, 2006). Descriptive statistics will be generated from survey data to characterize the distribution of scores on these measures.

VII. Risks and Discomforts

The anticipated risks associated with the proposed study are minimal. There is the potential for some subjects to experience discomfort in discussing psychiatric symptoms, including discussing craving for opioids. Participants will be reminded that they can choose to decline to answer any questions they do not wish to answer during the qualitative interviews, and will be reminded of the voluntary nature of study participation.
Another potential risk is a breach of confidentiality. However, as with the other risks mentioned above, we will take precautions to protect against this risk. Participants' names and other identifying information will be stored separately from other study materials, on a password-protected database. All other study materials (e.g., interview notes, self-report measures) will use a study ID number rather than identifying information, with the exception of the mobile apps: we will not enter <u>any</u> participant-specific information into the demonstration apps.

Participants will be fully informed of the nature of the risks involved during the informed consent process and will have the ability to discontinue and withdraw consent at any time. As part of the informed consent process, participants will be informed that if they feel uncomfortable responding to any question they are free to choose not to respond or to express their discomfort. Each participant will be made aware that participation is completely voluntary and that he or she may withdraw participation at any time without penalty. All study personnel will be trained in the appropriate care of human participants, will have completed Collaborative Institutional Training Initiative (CITI) program and will be closely supervised by the study PI. If a participant experiences distress at a higher level or longer duration than the mild to moderate, transient distress anticipated in study procedures, the PI will be contacted to determine whether intervention is indicated.

VIII. Potential Benefits

Participants are not expected to derive any direct benefit from this study. However, participation in this study will directly inform the development and finalization of an intervention to be tested in a future clinical trial. Assessment of participants' own lived experience of opioid use disorders, including craving, is essential to developing appropriate interventions for those with opioid use disorders. Thus, this study has the potential to improve future treatments for opioid craving.

IX. Monitoring and Quality Assurance

Dr. Peckham (a licensed clinical psychologist) will be responsible for continuous monitoring of the data and safety of subjects in the study. He will consult with other senior members of the study team (including Dr. Weiss – Chief of the Division of Alcohol, Drugs, and Addiction; and Dr.

McHugh, psychologist in the Division of Alcohol, Drugs, and Addiction) when any specific safety concerns arise. Dr. Peckham will monitor all survey and interview data as it is collected and will alert the IRB of any safety issues; minor deviations will be reported at annual continuing review in accordance with IRB guidelines.

X. References

Devilly, G. J., & Borkovec, T. D. (2000). Psychometric properties of the credibility/expectancy questionnaire. *Journal of Behavior Therapy and Experimental Psychiatry*, *31*(2), 73–86. https://doi.org/10.1016/S0005-7916(00)00012-4

Harris, P. A., Taylor, R., Thielke, R., Payne, J., Gonzalez, N., & Conde, J. G. (2009). Research electronic data capture (REDCap)-A metadata-driven methodology and workflow process for providing translational research informatics support. *Journal of Biomedical Informatics*, *42*(2), 377–381. https://doi.org/10.1016/j.jbi.2008.08.010

National Institutes of Health NIH HEAL Initiative Research. (March 18th, 2020). Retrieved from: https://heal.nih.gov/about/research-plan

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., … Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society*, *53*(4), 695–699. https://doi.org/10.1111/j.1532-5415.2005.53221.x

Preston, K. L., Kowalczyk, W. J., Phillips, K. A., Jobes, M. L., Vahabzadeh, M., Lin, J.-L., … Epstein, D. H. (2017). Exacerbated craving in the presence of stress and drug cues in drug-dependent patients. *Neuropsychopharmacology*, *43*(4), 859–867. https://doi.org/10.1038/npp.2017.275

Thomas, D. R. (2006). A general inductive approach for analyzing qualitative evaluation data. *American Journal of Evaluation*, *27*(2), 237–246. https://doi.org/10.1177/1098214005283748

Wiers, R. W. (2018). Cognitive training in addiction: Does it have clinical potential? *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, *3*, 101–102. https://doi.org/10.1016/j.bpsc.2017.12.008

Yardley, L., Morrison, L., Bradbury, K., & Muller, I. (2015). The person-based approach to intervention development: Application to digital health-related behavior change interventions. *Journal of Medical Internet Research*, *17*(1), e30. https://doi.org/10.2196/jmir.4055

Yardley, L., Spring, B. J., Riper, H., Morrison, L. G., Crane, D. H., Curtis, K., … Blandford, A. (2016). Understanding and promoting effective engagement with digital behavior change interventions. *American Journal of Preventive Medicine*, *51*(5), 833–842. https://doi.org/10.1016/j.amepre.2016.06.015